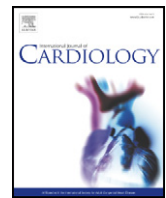




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Repetitive use of levosimendan for treatment of chronic advanced heart failure: Clinical evidence, practical considerations, and perspectives: An expert panel consensus



M.S. Nieminen^{a,*}, J. Altenberger^b, T. Ben-Gal^c, A. Böhmer^d, J. Comin-Colet^e, K. Dickstein^f, I. Édes^g, F. Fedele^h, C. Fonsecaⁱ, M.J. García-González^j, G. Giannakoulas^k, Z. Iakobishvili^l, P. Jäskeläinen^m, A. Karavidasⁿ, J. Kettner^o, M. Kivikko^p, L.H. Lund^q, S.T. Matskeplishvili^r, M. Metra^s, F. Morandi^t, F. Oliva^u, A. Parkhomenko^v, J. Parissis^w, P. Pollesello^p, G. Pözl^x, R.H.G. Schwinger^y, J. Segovia^z, M. Seidel^{aa}, B. Vrtovec^{ab}, G. Wikström^{ac}

^a Helsinki University Hospital, Helsinki, Finland

^b Pensionsversicherungsanstalt SKA-RZ Großmain für Herz-Kreislauf- und neurologische Erkrankungen, Lehrkrankenhaus der Paracelsus Medizinischen Privatuniversität, Großmain, Austria

^c Heart Failure Unit and Heart Transplant Clinic, Rabin Medical Center, Petah Tikva, Israel

^d LK Krems, Abteilung für Innere Medizin mit kardiologischem Schwerpunkt, Krems, Austria

^e Heart Failure Program, Cardiology Department, Hospital del Mar, Barcelona, Spain

^f Stavanger University Hospital, University of Bergen, Stavanger, Norway

^g Institute of Cardiology, Medical and Health Center, University of Debrecen, Debrecen, Hungary

^h Department of Cardiovascular, Respiratory, Nephrology and Geriatric Sciences, 'La Sapienza' University of Rome, Rome, Italy

ⁱ Heart Failure Unit, Hospital S. Francisco Xavier/CHLO, Faculdade de Ciências Médicas Universidade Nova de Lisboa, Lisbon, Portugal;

^j Department of Cardiology, Hospital Universitario de Canarias, San Cristóbal de La Laguna, Sta. Cruz de Tenerife, Spain

^k Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece

^l Emergency Cardiology Services, Cardiac Intensive Care Unit, Beilinson Hospital, Rabin Medical Center, Petah Tikva, Israel

^m Heart Center, Kuopio University Hospital, Kuopio, Finland

ⁿ Cardiology Clinic of the Gennimatas General Hospital of Athens, Athens, Greece

^o Institut klinické a experimentální medicíny klinika kardiologie IKEM, oddělení akutní kardiologie KK IKEM, Vídeňská, Prague, Czech Republic

^p Orion Pharma, Espoo, Finland

^q Unit of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

^r Scientific Centre of Cardiovascular Surgery of Bakulev, Moscow, Russia

^s Cardiology Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy

^t Department of Cardiovascular Science, University of Insubria, Circolo Hospital and Macchi Foundation, Varese, Italy

^u 'A. De Gasperi' Cardiac Failure and Transplantology Department, Niguarda Ca'Granda Hospital Milan, Milan, Italy

^v Strazhesko Institute of Cardiology, National Scientific Centre, Kiev, Ukraine

^w Second Cardiology Department and Heart Failure Unit, Attikon Teaching Hospital, Athens, Greece

^x Department of Internal Medicine III, University of Innsbruck, Austria

^y Medizinische Klinik II, Klinikum Weiden, Akademisches Lehrkrankenhaus der Universität Regensburg, Germany

^z Unidad de Insuficiencia Cardíaca, Trasplante e Hipertensión Pulmonar, So. Cardiología, Hospital Univ. Puerta de Hierro, Madrid, Spain

^{aa} Unfallkrankenhaus Berlin, Klinik für Innere Medizin, Berlin, Germany

^{ab} Clinical Department of Cardiology, University Clinical Centre Ljubljana, Ljubljana, Slovenia

^{ac} Cardiology, Institute of Medical Sciences, Uppsala University, Uppsala, Sweden

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ABSTRACT

Background: The intravenous inodilator levosimendan was developed for the treatment of patients with acutely decompensated heart failure. In the last decade scientific and clinical interest has arisen for its repetitive or intermittent use in patients with advanced chronic, but not necessarily acutely decompensated, heart failure. Recent studies have suggested long-lasting favourable effects of levosimendan when administered repetitively, in terms of haemodynamic parameters, neurohormonal and inflammatory markers, and clinical outcomes. The existing data, however, requires further exploration to allow for definitive conclusions on the safety and clinical efficacy of repetitive use of levosimendan.

Methods and results: A panel of 30 experts from 15 countries convened to review and discuss the existing data, and agreed on the patient groups that can be considered to potentially benefit from intermittent treatment with levosimendan. The panel gave recommendations regarding patient dosing and monitoring, derived from the available evidence and from clinical experience.

* Corresponding author at: Head of Heart and Lung Center, University of Helsinki Central Hospital, Helsinki, Finland. Tel.: +358 400443076.
E-mail address: markku.nieminen@hus.fi (M.S. Nieminen).

Conclusions: The current data suggest that in selected patients and support out-of-hospital care, intermittent/repetitive levosimendan can be used in advanced heart failure to maintain patient stability. Further studies are needed to focus on morbidity and mortality outcomes, dosing intervals, and patient monitoring. Recommendations for the design of further clinical studies are made.

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1. Introduction

Advanced heart failure (HF) is characterised by repeated episodes of cardiac decompensation, frequent and prolonged hospitalisation, and severely compromised patient quality of life [1]. The ageing of the population and the availability of improved life-prolonging treatment options are contributing to an increase in the burden of chronic advanced HF [2]. The rising prevalence of this end-stage HF is not only associated with substantial morbidity and mortality, but also causes significant health-care expenditure due mostly to repeated hospitalisations [3,4]. At each successive admission for exacerbation of HF, the patient leaves the hospital with a more pronounced decrease in cardiac function and a higher probability of further rehospitalisation at shorter intervals, as well as of death [5].

In the past, some studies have suggested that continuous or intermittent infusion of parenteral dobutamine or milrinone as inotropic support could provide favourable effects to support the circulation and heart function in long-term therapy of end-stage HF [6–12]. Such continuous or intermittent use of these traditional inotropic drugs has remained, however, sporadic due to the evidence of increased risk of mortality [13]. In this regard, two focused meta-analyses by Tacon et al. [14] and by Nony et al. [15] were published which investigate the use of dobutamine and phosphodiesterase inhibitors, respectively, both failing to show any benefit by those drugs.

In the early 2000s, a new drug became available for the treatment of acutely decompensated HF, the inodilator levosimendan [16–18]. The clinical data for levosimendan, which combines positive inotropic, vasodilatory, and cardioprotective effects but does not evoke significant changes in oxygen requirements, were recently reviewed [19]. In the last five years, there have been ten meta-analyses on the clinical data of levosimendan from independent research groups [20–29], all of which suggest a possible advantage of levosimendan in various clinical settings.

In the last three editions of the European Society of Cardiology (ESC) guidelines for the treatment of HF levosimendan was included in the armamentarium of drugs that are available for the treatment of acute HF [1,30,31]. In the recent literature and in clinical practice, there has been interest in the use of i.v. levosimendan in chronic advanced HF, also for planned repetitive use to potentially avoid acute decompensation and frequent rehospitalisation and possibly improve other outcomes.

A panel of 30 experts from 15 countries (Austria, Czech Republic, Finland, Germany, Greece, Hungary, Israel, Italy, Norway, Portugal, Russia, Slovenia, Spain, Sweden, and Ukraine) convened in Munich on 17 October, 2013 to: (a) review the existing literature on planned intermittent treatment with levosimendan for patients with chronic advanced HF; (b) agree on the patient groups that can be considered to benefit most from this treatment; (c) outline preliminary recommendations for the use of planned intermittent treatment with levosimendan for the management of these patients; and (d) suggest further studies or meta-analyses. This consensus paper presents the conclusions of this expert panel.

2. Pharmacokinetic and pharmacodynamic effects of levosimendan

Levosimendan provides both rapid and sustained effects, with the rapid effects mediated by the parent drug, levosimendan, and the sustained effects mediated by its active metabolite OR-1896 [32]. While the half-life of levosimendan is 1.3 h, the plasma concentration of OR-

1896 reaches its peak 2–3 days after levosimendan infusion. As the effects of OR-1896 closely resemble those of levosimendan [33,34], the parent-drug-related effects are carried forward. Pronounced haemodynamic effects are seen within 1 h of bolus administration of levosimendan (usually 6–12 µg/kg over 10 min). However, this use of bolus administration can induce untoward effects, such as hypotension and tachycardia, and should thus only be used if an immediate response is required, and if the patient risk/benefit ratio is judged to be favourable [35].

After a 24-h infusion of levosimendan, its pharmacodynamic effects (i.e., on cardiac output and pulmonary capillary wedge pressure) persist for at least a week [36]. In the REVIVE II trial, which compared levosimendan (bolus of 6–12 µg/kg over 10 min followed by 0.1–0.2 µg/kg/min for 24 h) with placebo, on top of standard of care, in patients with acutely decompensated HF, the percentage of patients free of dyspnoea favoured levosimendan over placebo, for up to 5 days after the completion of treatment [37].

Pharmacokinetic data pertaining to 6-h infusions of levosimendan are limited. In patients with pulmonary hypertension, assessment of their pulmonary vascular resistance showed that a 6-h infusion is not sufficient to maintain the clinical effects of levosimendan for 2 weeks [38].

In man, the formation of the levosimendan metabolite OR-1896 depends on the acetylation status of the patient, whereby rapid acetylators produce higher quantities of OR-1896 [39]. Contrary to the assumption that rapid acetylators should experience more pronounced haemodynamic effects after levosimendan infusion, the efficacy of levosimendan appears not to be affected by the patient acetylation status [40].

3. Long-term effects of levosimendan on cytokines and neurohormones

Heart failure is a systemic condition in which neurohormonal and inflammatory activation mediates cardiac remodelling and clinical progression [41]. Sustained neurohormonal and anti-inflammatory effects of levosimendan have been shown in patients with advanced HF. In patients with reduced left ventricular ejection fraction (LVEF), levosimendan can reduce the brain natriuretic peptide (BNP) levels, which parallels the improvement in systolic and diastolic functions [42]. These BNP-lowering effects of levosimendan are significantly more pronounced and prolonged than those of dobutamine [43].

According to two studies, levosimendan induces reductions in TNF-α and IL-6 levels [44,45], which is not the case for dobutamine or placebo [44]. Moreover, proapoptotic factors like sFas and Fas-ligand are significantly reduced for extended periods of time [44,45]. Levosimendan inhibits the release of reactive oxygen species in polymorphonuclear leukocytes in vitro and in patients with acute HF and septic shock [46]. Endothelial function is substantially improved in advanced chronic HF [47], which might explain the beneficial effects of levosimendan on coronary blood flow that have been seen in previous haemodynamic [48,49] and echocardiographic [50,51] studies.

Furthermore, a meta-analysis of randomised controlled studies showed that the release of troponin after cardiac surgery was lower in levosimendan-treated patients than in the control groups [52]. In addition, levosimendan improved right ventricular function in patients with advanced HF [53]. Due to these effects, hepatic congestion can be improved in patients with acute decompensated HF, according to a sub-analysis of the SURVIVE study [54].

Table 1
Clinical trials that have assessed the repetitive use of levosimendan.

Study (Ref)	Patients, study design	Comparator	Planned cumulative dose ($\text{mg} \times \text{kg}^{-1}$)	Number of cycles/duration	Length of treatment (+ follow up)	Main results described
Altenberger et al. [62]	120, randomised	LS vs placebo	Up to 0.29	4/6 h/bi-weekly	6 weeks (+20 weeks)	Primary endpoint not met, secondary endpoint (morbidity and mortality) met
Malfatto et al. [61]	33, not randomised	LS vs furosemide	Up to 2.11	4/24 h/monthly	3 months (+1 month + 1 year)	Favourable effects on LVEF, neurohormonal balance and 1-year survival
Bonios et al. [60]	63, randomised	LS vs dobutamine vs Dob + LS	2.92	24/6 h/weekly	6 months	Survival and haemodynamic benefits
Mavrogeni et al. [57]	50, randomised, open	LS vs placebo	1.73	6/24 h/monthly	6 months	Improvement in symptoms and LVEF
Nanas et al. [55]	36, open	LS + dobutamine vs dobutamine alone	1.15	4/24 h/bi-weekly	6 weeks (+3 days)	Improvement in 45-day survival rate
Parissis et al. [56]	25, randomised	LS vs placebo	0.75 to 2.66	5/24 h/3-weekly	12 weeks (+30 days)	Improvement in LVEF, modulation of neurohormonal and immune activation
Berger et al. [58]	75, randomised	LS vs prostaglandin E1	Up to 0.62	4/24 h/monthly	3 months (+9 months)	Inferior facilitation of up-titration of beta-blockers and worse clinical outcome, equal effect on mortality.
Papadopoulos et al. [59]	30, open	LS (no comparator)	0.86	6/24 h/monthly	6 months	Improvement in objective echocardiographic measures and subjective quality-of-life questionnaires
Kleber et al. [38]	28, randomised	LS vs placebo	Up to 0.58	1 × 24 then 4 × 6 h bi-weekly	8 weeks (+4 weeks)	Improvement in pulmonary vascular resistance and mean pulmonary artery pressure

Cumulative dose (in $\text{mg} \times \text{kg}^{-1}$) is calculated by multiplying the infusion rate (e.g. $0.2 \mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$) with the time of a single infusion (e.g. 24 h, i.e. 1440 min) and with the number of repeated infusions (e.g. 4). Use of bolus and up-titration times are also taken into account. As an example, a cumulative dose of 1 mg/kg corresponds to 6 vials of levosimendan (a 12.5 mg) for a 75-kg patient.

4. Previous studies with repetitive levosimendan use

The following search strategy was used to find previous studies on repetitive or intermittent use of levosimendan. Medline and Embase (1990 to 15 October, 2013) were searched via an Ovid interface: [Levosimendan] AND [repetitive OR intermittent]. The search was limited to English language and human. Twelve references were found, nine of which were considered to be relevant to the subject under discussion (see Table 1). No relevant Cochrane reviews were identified at the moment of the search.

Nanas et al. [55] compared the efficacy and safety of bi-weekly levosimendan added to daily dobutamine infusion versus daily dobutamine infusions alone in patients who were refractory to an initial 24-h dobutamine infusion. This prospective trial was open label and the treatment assignment was not randomised, but instead sequential. Intermittent levosimendan infusions dramatically increased patient survival, with 61% vs. 6% of the patients still alive at 45 days.

Levosimendan every 3 weeks was compared with placebo by Parissis et al. [56] In 25 patients with advanced chronic HF, levosimendan promoted significant improvements in LVEF, levels of the N-terminal prohormone of brain natriuretic peptide (NTproBNP) and IL-6, and end-systolic stress (as measured by echocardiography), without increasing myocardial injury, according to troponin T measurements.

Mavrogeni et al. [57] showed significant symptom improvement and increases in left ventricular systolic function, as well as a reduction in mortality, with intermittent monthly infusions of levosimendan over 6 months, compared to standard care. LVEF improved significantly, as did end-diastolic and end-systolic volumes. On the other hand, in the trial by Berger et al. [58], patients with intolerance to the appropriate beta-blocker therapy benefited to a greater extent from continuous treatment with prostaglandin E1 than from 24-h levosimendan at 4-weekly intervals, with regard to up-titration of beta-blockers. The composite end-point of HF worsening, death, urgent heart transplantation, and/or implantation of left ventricular assist device was also in favour of prostaglandin E1 (11% vs. 31% for levosimendan, $p = 0.04$). In this study by Berger et al., [58] two patients per group died during the 12-week treatment (5% vs. 6% for levosimendan and comparator, respectively; n.s.) and at the end of the 1-year follow-up, 6 patients had died in the levosimendan group versus 7 in the control group (n.s.).

Papadopoulos et al. [59] demonstrated improvements in both objective echocardiographic measurements and subjective quality of life measures with 24-h levosimendan, although they did not have a comparator group. Kleber et al. [38] assessed repetitive levosimendan treatment in 28 patients with pulmonary hypertension, with most of them suffering from systolic HF. Compared to placebo, levosimendan reduced pulmonary vascular resistance and mean pulmonary artery pressure to a significantly greater extent. During the study, one patient died in the placebo group and none in the levosimendan group.

In the randomised study by Bonios et al. [60], 63 patients with decompensated end-stage HF refractory to standard therapy were randomised to levosimendan, dobutamine, or levosimendan plus dobutamine after stabilisation and successful weaning from initial inotropic agents. A highly significant benefit was observed for the event-free survival with levosimendan only, while patients who received the combination fared worst. At 6 months, the mortality rate was 19% in the levosimendan arm, 38% in the dobutamine arm ($p = 0.037$ vs. levosimendan), and 48% in the combination arm ($p = 0.009$ vs. levosimendan).

Monthly levosimendan was compared with furosemide by Malfatto et al. [61] The levosimendan therapy resulted in significant reductions in New York Heart Association (NYHA) classes and improvements in echocardiographic parameters and BNP levels. In the levosimendan group, 1-year mortality tended to be lower than in the control group (18.2% vs. 36.4%, respectively).

The prospective, multicentre, randomised, placebo-controlled, double-blind, two-armed, parallel-group LevoRep Study was the largest

trial on repetitive, ambulatory administration of inotropes for end-stage HF [62,63]. Overall, 120 patients with chronic stable HF, as NYHA III/IV for >3 months, LVEF $\leq 35\%$, and 6-min-walk distance <350 m, received individually optimised neurohormonal background therapy and were randomised to placebo or levosimendan 0.2 $\mu\text{g/kg/min}$ for 6 h at 2-week intervals for a total of 4 infusions. The combined primary endpoint was for improvement in functional capacity of $\geq 20\%$ according to the 6-min-walk test, plus improvement in patient quality of life of $\geq 15\%$ as assessed by the Kansas City Cardiomyopathy Questionnaire score. At the end of the 24-week follow-up, the primary endpoint was not reached, despite a non-significant positive trend in favour of levosimendan. However, the study met its secondary end-points: compared to placebo, ambulatory levosimendan was safe and improved event-free survival (defined as freedom from death of all causes, heart transplant/ventricular assist device [VAD] implantation or acute HF) by 50% in the long term (24 weeks). This favourable effect was accompanied by NT-proBNP decreases of $\leq 30\%$ in nearly half of the patients at 8 weeks. Across both of these arms, similar percentages of patients experienced adverse events. The potential reasons for missing the primary endpoint in this LevoRep study include under-dosing of the study drug (see comparison of cumulative doses in various studies in Table 1), insufficient size of the study population, and favourable effects in the placebo arm due to the high quality of care. Also, the combined endpoint might have been too ambitious. Although caution should be exercised in interpreting favourable effects in secondary outcomes, the reduction in event-free survival is promising.

Finally, it is worth mentioning that Parle et al. [64] reported data on repeated infusions of levosimendan in patients with decompensated HF, collected in a single-centre, prospective, non-randomised study. Here, the 44 patients received levosimendan from 2 to 26 times, with a mean dosing interval of 66.2 ± 12 days. Levosimendan was considered to have been well tolerated and to have improved functional capacity.

A meta-analysis on the effects on mortality of repetitive use of levosimendan versus any comparator in patients with advanced HF was performed by selecting studies that had reported mortality at the end of the follow-up period (7 of the 9 studies listed in Table 1). The data on outcome extracted from those papers were analysed with RevMan 5.2 (freeware available from The Cochrane Collaboration) [65]. The analysis showed a significant reduction in mortality, with a risk ratio of 0.47 [0.32–0.70] ($p = 0.0002$) and a low heterogeneity (Fig. 1).

During the revision of the present manuscript, a new meta-analysis on the effects of levosimendan on mid-term survival in chronic heart failure patients was published [66] in which levosimendan was associated with a significant reduction in mortality at the longest follow-up available [32 of 168 (19%) in the levosimendan group 46 of 133 (35%) in the control arm, RR = 0.55 (95% CI 0.37–0.84), p for effect = 0.005, p for heterogeneity = 0.3, $I^2 = 23.4\%$, NNT = 6, with 5 studies included].

In an overall analysis, it appears that, the existing literature on the repetitive use of levosimendan is not uniform. The studies vary in their control arm (placebo, diuretics, dobutamine), and for the dose and the interval of levosimendan administration, the designs, and the selection of primary and secondary outcome measures. It appears also, however, that a general positive trend in favour of the repetitive use of levosimendan is present. For this reason we performed our meta-analysis of the mortality data. Since the meta-analysis is based on few mortality events (24 in the levosimendan group vs. 49 in the control group) any conclusion based on it should only be taken as hypothesis generating.

On the other hand, also in the meta-analysis by Silvetti et al. [66] the authors show a general homogeneity in the mortality results among the studies, and a low risk of bias (as shown by the funnel plot). Moreover, their result is still significantly in favour of levosimendan although they did not introduce in their calculation the data of Nanas et al. [55], a

sequential clinical study which, in our own calculation, contributes for 44% of the events.

5. On-going trials

At present, intermittent dosing of levosimendan is being assessed in a double-blind fashion in the LION-HEART, LAICA and ELEVATE studies (Table 2).

The LION-HEART trial is evaluating the safety and efficacy of repetitive 6-h doses of levosimendan every 2 weeks, as compared to placebo. The primary endpoint is the change in NT-proBNP levels between baseline and end of treatment, 12 weeks later.

The LAICA study is assessing the effects of intermittent repeated levosimendan every 30 days (for 1 year) on combined overall mortality rate and hospital admission rate for acute cardiac decompensation or HF worsening [67]. A sub-study is evaluating the treatment effects on renal function, while another sub-study is focused on the cost-effectiveness.

The ELEVATE study aims to investigate the effects of levosimendan versus diuretics on hospitalisation-free survival, with the treatment applied in patients with early signs of decompensation for impending destabilisation.

6. Recommendations on intermittent levosimendan therapy

Repetitive use of levosimendan as referred to here is defined as “scheduled” repeated or intermittent administration. Based on the results of the studies described above, it appears reasonable to provide recommendations for such use of levosimendan in selected patients, at certain doses, and with due monitoring, with the aim of improving hemodynamic stability, reducing clinical markers and symptoms, and possibly mortality and hospitalisation for acute deterioration of cardiac function.

6.1. Identification of the Advanced Heart Failure population

It can be challenging to define advanced or end-stage HF due to the natural fluctuations in the later stages of this disease. However, some useful criteria have been provided by various boards. In a position statement published in 2007, the Study Group on Advanced Heart Failure of the Heart Failure Association of the ESC indicated six criteria for the definition of advanced chronic HF [68], and these have become widely accepted (see Table 3).

The study group made a distinction between advanced chronic HF and end-stage HF: while cardiac dysfunction and symptoms are potentially reversible in advanced chronic HF, in end-stage HF, they are not. Furthermore, the ESC position paper defines the criteria for severe cardiac dysfunction. These are applied on the assumption that optimal treatment that includes beta blockers, angiotensin-converting enzyme inhibitors, diuretics including aldosterone antagonists, and cardiac resynchronization therapy (CRT), if indicated, has already been initiated, without any further response.

These clinical criteria for the identification of patients with advanced HF (Table 3) are also included in the 2013 American College of Cardiology Foundation/American Heart Association guidelines [69]. These encompass factors such as NYHA 3+ to 4 class heart failure, repeated (≥ 2) hospitalisation or Emergency Department visits for HF in the past year, progressive deterioration in renal function, weight loss without other causes, intolerance to angiotensin-converting enzyme inhibitors or beta blockers, frequent systolic blood pressure <90 mm Hg, and exercise intolerance.

6.2. Indications for repetitive levosimendan use

In the framework of the patient population described in the previous paragraph, and according to the published studies (Table 1, Fig. 1), the panel reached a consensus for the definition of potential indications

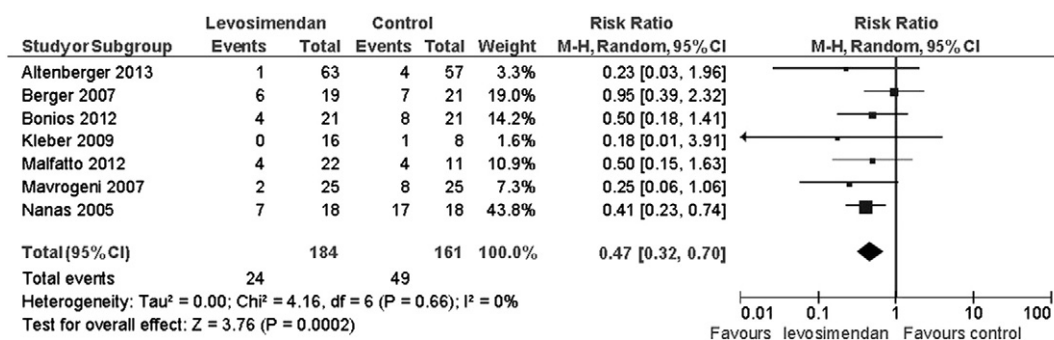


Fig. 1. Meta-analysis: reduction in mortality rates using repetitive levosimendan therapy.

for repetitive use of levosimendan in chronic advanced HF. This high-risk setting is as listed in Table 4.

As an example, suitable patients are both those listed for heart transplantation or waiting for VAD implantation, and those with similar characteristics but who are not eligible (palliative). The treatment goals differ, however, between these two groups. While the preservation of organ function (e.g., renal and hepatic function) should be achieved as a bridging measure in patients who are scheduled for transplantation or VAD implantation, the stabilisation and well-being of the patients, and their avoidance of re-hospitalisation, represent the most important goal in the palliative setting. Although this has not been studied specifically, repetitive levosimendan use can potentially contribute to reduction in the emergency transplantation rate, as well as in the rate of patients dying on the transplantation list. If circumstances permit, intermittent levosimendan therapy might ideally be conducted on an outpatient basis (as in the LevoRep study [62]).

In clinical follow-up, caution must be taken regarding the possible adverse effects of levosimendan on systolic blood pressure, and potentially on arrhythmias. Risk assessment should always precede initiation of therapy. The patients should receive optimal medical background therapy. Prolonged hypotension should be avoided.

Standard cardiac procedures should not be unduly delayed or neglected because of the availability of intermittent medical treatment; i.e. this is not a substitute for VAD, CRT, transplantation, or other interventions in the treatment of patients with chronic advanced HF. Before initiating repetitive use of levosimendan, baseline NT-proBNP and echocardiography are helpful.

6.3. Dosing

As patient characteristics and needs vary considerably, as well as their responses to treatment, we recommend the flexible dosing of 0.05 $\mu\text{g}/\text{kg}/\text{min}$ to 0.2 $\mu\text{g}/\text{kg}/\text{min}$, for 6 h to 24 h, every 2 weeks to 4 weeks. Treatment can be started with low dosing, and can be increased stepwise during the remaining time up to 24 h. Hypotension and arrhythmias were described as adverse events in the two Phase III clinical studies SURVIVE [70] and REVIVE [37]. Both of these studies included bolus levosimendan dosing and relatively high maintenance

infusion rates. These factors might have predisposed the patients to these adverse events. Therefore, it is believed that bolus levosimendan application should only be administered if immediate effects are required and if systolic blood pressure exceeds 100 mm Hg. Furthermore, the maintenance infusion rate might need to be down-titrated if such adverse events occur. In the case of intermittent application, the use of bolus levosimendan is thus not recommended. Hypokalaemia and hypovolaemia should be avoided before and during treatment.

6.4. Monitoring

For safety purposes, the monitoring of blood pressure, heart rate, body weight, serum sodium and potassium levels, and serum creatinine levels is recommended when i.v. levosimendan is administered.

In general, a systolic blood pressure of 85 mm Hg to 100 mm Hg does not rule out treatment with repetitive use of levosimendan, although there should be close monitoring according to the patient profile. The volemic status of the patient must be carefully evaluated when i.v. levosimendan is administered and, in the case of hypovolemia, fluid substitution during infusion might be needed. In the case of more severe hypotension the dose of levosimendan might need to be temporarily reduced and/or a vasopressor added (e.g. noradrenaline). An intense diuresis as a result of levosimendan treatment might be seen in some patients. The elimination or reduction of the regular diuretic on the day of treatment should thus be considered, and additional fluid given as needed.

Kidney function assessment is of interest in patients with known renal dysfunction and in those on diuretic treatment. While secondary renal dysfunction does not preclude treatment with repetitive use of levosimendan (see Yilmaz et al. [71]), caution should be exercised in patients with intrinsic kidney failure.

Due to the individual nature of the course of chronic advanced HF, there can be no universal recommendations relating to a glomerular filtration rate (GFR) cut-off with regard to repetitive levosimendan use. However, a GFR of ~ 30 mL/min/1.73 m² [2] might constitute a certain safety threshold [72].

If furosemide is administered concurrently, the doses should be adjusted. Omitting or reducing the diuretic treatment for the morning

Table 2
Ongoing trials that are assessing intermittent or repetitive levosimendan treatment.

Name of the trial (acronym, NCT code)	Expected N (design)	Dose ($\mu\text{g} \times \text{kg}^{-1} \times \text{min}^{-1}$)	Infusion Length (h)	Treatments (study duration)
The Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients study (LION-HEART, NCT01536132)	69 (1:1 vs placebo)	0.2	6	Every two weeks (per 3 months)
The Randomised, Double-blind, Placebo-controlled, Multicentre Trial to Study Efficacy, Security, and Long-term Effects of Intermittent Repeated Levosimendan Administration in Patients with Advanced Heart Failure (LAICA, NCT00988806)	213 (1:1 vs placebo)	0.1	24	Every 15 or 30 days (per 12 months)
The Early LEvosimendan Versus Usual Care in Advanced Chronic heart failure (ELEVATE, NCT01290146)	134 (1:1 vs furosemide)	0.05 or 0.1	24	At early signs of deterioration (per 12 months)

Table 3

Criteria for the definition of advanced chronic heart failure indicated by the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology [67].

Definition of advanced heart failure
Severe symptoms of heart failure (NYHA class III or IV)
Episodes of fluid retention and/or peripheral hypoperfusion
Objective evidence of severe cardiac dysfunction
Severe impairment of functional capacity
History of ≥ 1 heart failure hospitalisation in the past 6 months
Presence of all of the previous features despite “attempts to optimise” therapy

before levosimendan therapy can help to avoid sudden drops in blood pressure and the ensuing renal complications. Where there is an intention to deliver therapy in an outpatient setting, we recommend that the first administration(s) of levosimendan are performed in hospital (ideally day-hospital), with monitoring of blood pressure and heart rate.

The agenda and intervals of monitoring visits should be determined according to the individual patient risk assessment.

Other guidance measures for these patients on repetitive levosimendan therapy include counselling on diet and exercise/daily activity/rest, as well as quality-of-life evaluation. Ideally, trained HF nurses can perform these tasks in global HF management programme settings, according to standardised protocols. The application of the interval of 2–4 weeks should be triggered by the increasing symptoms of the patient.

7. Potential future studies/registries

There is definitely a need for more solid data on hospitalisation and mortality rates associated with repetitive use of levosimendan.

The three studies that are on-going (see above) should certainly shed some light on the effects of such treatment on long-term clinical outcome. When these data join the data pool, the present open questions might be answered, based on the substantial patient numbers. Moreover, if the interim results of LAICA are promising, expansion of the study to other centres in Europe is conceivable. In turn, the extended data pool might give rise to distinct questions that can be addressed in a prospective manner. A parallel approach might be analyses on the basis of registries, such as the Swedish Heart Failure Registry [73].

8. Conclusions

Overall, patients with chronic advanced HF constitute a relatively small, but important, population that faces substantial morbidity with frequent hospitalisation and high mortality. Substantial treatment costs contribute to the great burden caused by chronic advanced HF. A subset of these patients will continue to progress and develop more severe symptoms despite optimal therapy. For this group, repetitive levosimendan therapy might represent a comparatively safe and effective treatment option.

Levosimendan has now been in extensive clinical use for over 10 years. Using levosimendan intermittently is a novel approach that has raised interest within the medical community. To date, nine studies that have included more than 500 patients have evaluated repetitive use

of levosimendan in patients with chronic advanced HF. Disparities in patient selection and in study design and follow-up render this comparison and any firm conclusions from these trials difficult; nonetheless, benefits of the repetitive use of levosimendan have been demonstrated.

There is evidence showing improvements in haemodynamics, symptoms, rehospitalisation rates, and biomarkers. The issue of mortality, however, remains to be resolved, which will require further studies. Thus, our suggestions must be taken with caution and in full respect of the local guidelines. The trials that are ongoing will add valuable information to the existing data.

Conflicts of interest

This project did not receive any financial support, apart from logistic expenses related to the organisation of the consensus meeting in Munich on 17 October, 2013, which were covered by Orion Pharma. Attendees were invited by the chairman (MSN) on the basis of their experience with repetitive use of levosimendan documented in the literature. The attendees did not receive any honorarium. In the past 5 years, MSN, JA, JC-C, IÉ, FF, LHL, AP, JP, GP, and GW have received research grants or limited lectures honoraria from Orion Pharma. PP and MK are employees of Orion Pharma. Orion Pharma follows the code of conduct of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

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Table 4

High-risk setting defining the patients who could benefit from repetitive use of levosimendan in chronic advanced HF.

Indication for levosimendan use in advanced heart failure
• Severe systolic dysfunction (LVEF <35%)
• and/or NYHA IIIb–IV and/or INTERMACS levels 4, 5, 6
• and/or Repeated hospitalisation or emergency department visits (≥ 2 in the past year)
• All of the above despite optimal treatment for heart failure

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